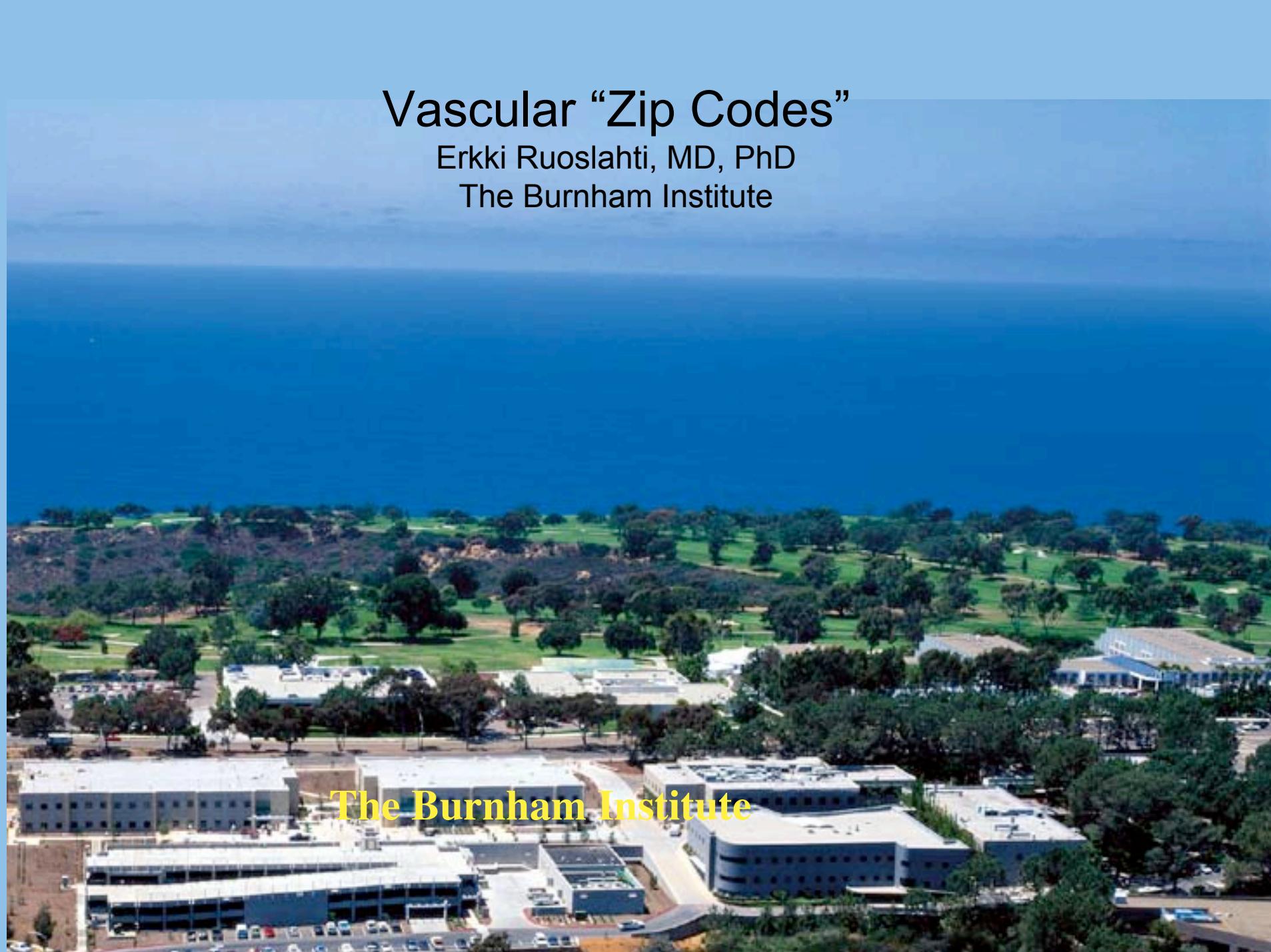


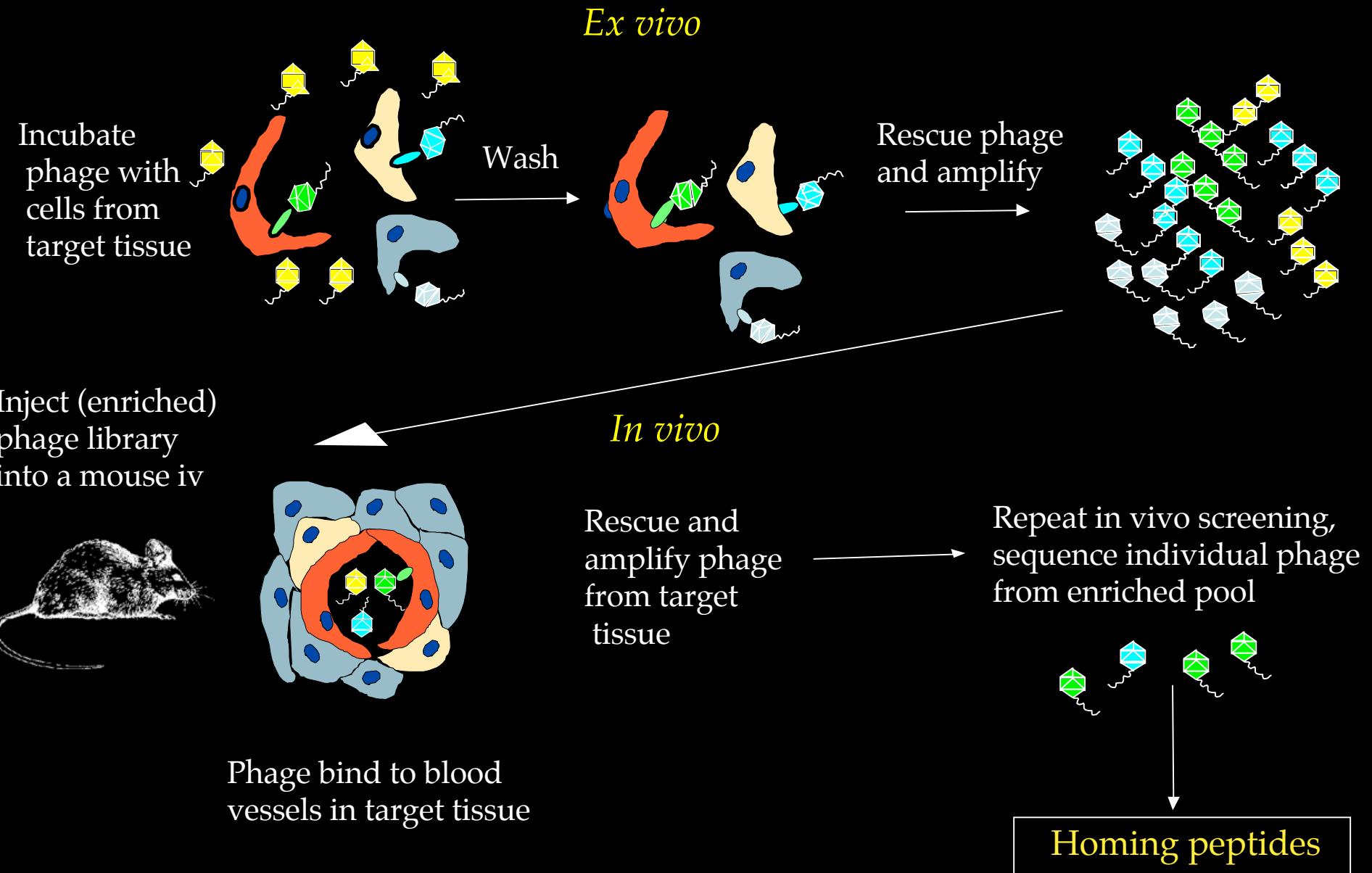
Vascular “Zip Codes”

Erkki Ruoslahti, MD, PhD
The Burnham Institute

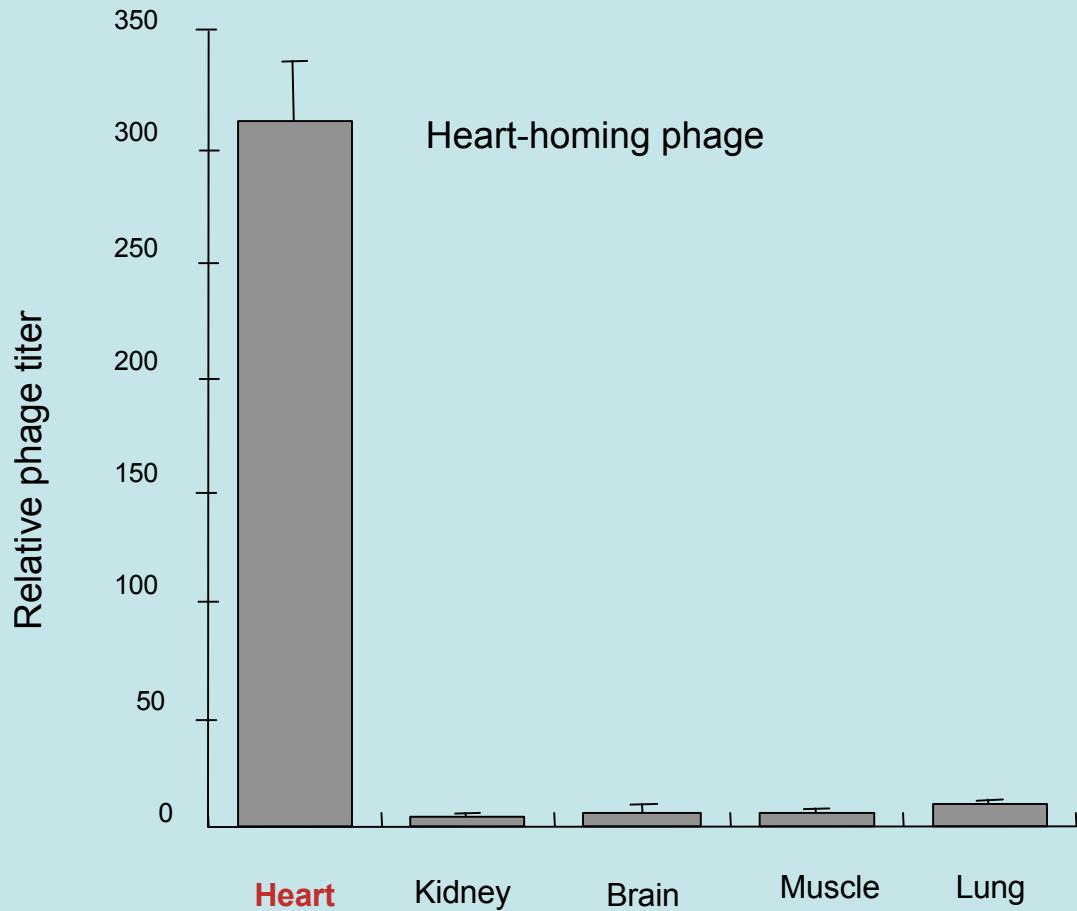


The Burnham Institute

Isolation of homing peptides by *ex vivo/in vivo* phage screening



The blood vessels in individual tissues are distinct



Normal tissues targeted with vascular homing peptides:

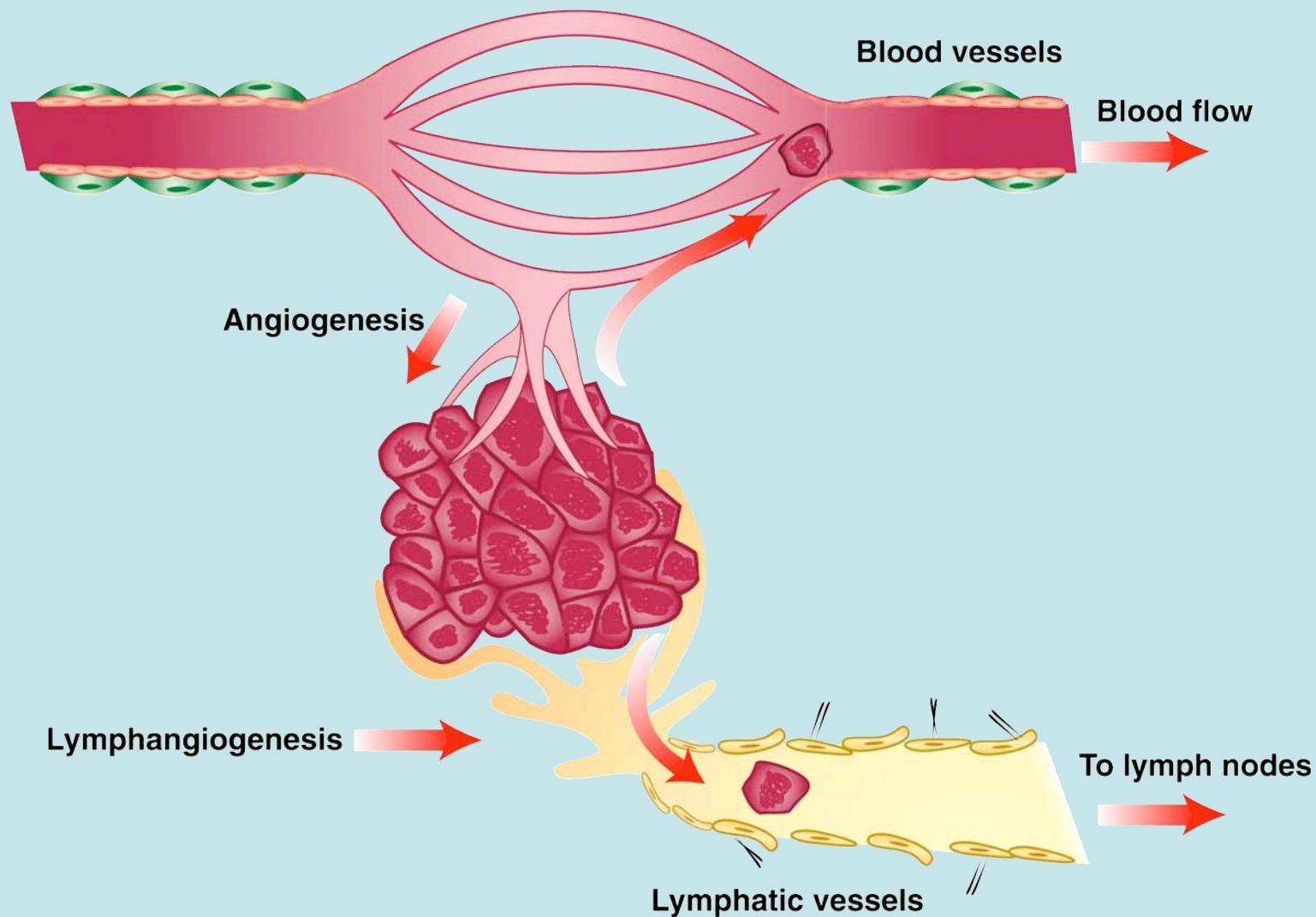
Brain
Kidneys
Lungs
Prostate
Skin
Breast
Muscle
Pancreas
Adrenals
Uterus
Liver
Heart

- Bacterial 2-hybrid screen for receptors

L. Zhang et al. *Circulation*, 2005

Tumor-homing Peptides

Peptide	Sequence	Specificity	Receptor	Reference
Blood Vessels				
RGD-4C	CDCRGDCFC	Angiogenic endothelium	$\alpha_v\beta_3$ and $\alpha_v\beta_3$ integrins	Arap et al., <i>Science</i> , 1998
F3	34-amino acid basic peptide	Angiogenic endothelium, tumor cells	Cell surface nucleolin	Porkka et al., 2002; Christian et al., 2003
CGKRK	CGKRK	Angiogenic endothelium, tumor cells	Heparan sulfate?	Hoffman et al., 2003
Lymphatic Vessels				
LyP-1	CGNKRTRGC	Breast ca lymphatics, tumor cells	Not known	Laakkonen et al., 2002; 2004
LSD		Melanoma lymphatics	CXCR4?	Zhang et al, submitted
REA		Prostate ca lymphatics, tumor cells		Zhang et al, submitted
Vessel/Tumor ECM				
CREKA	CREKA	Breast ca extracellular matrix	Not known	Essler et al., unpublished
Plasma Clot				
CLTI	10-amino acid cyclic peptide	Blood clots, fibrin deposits in tumors	Not known	Pilch et al., unpublished

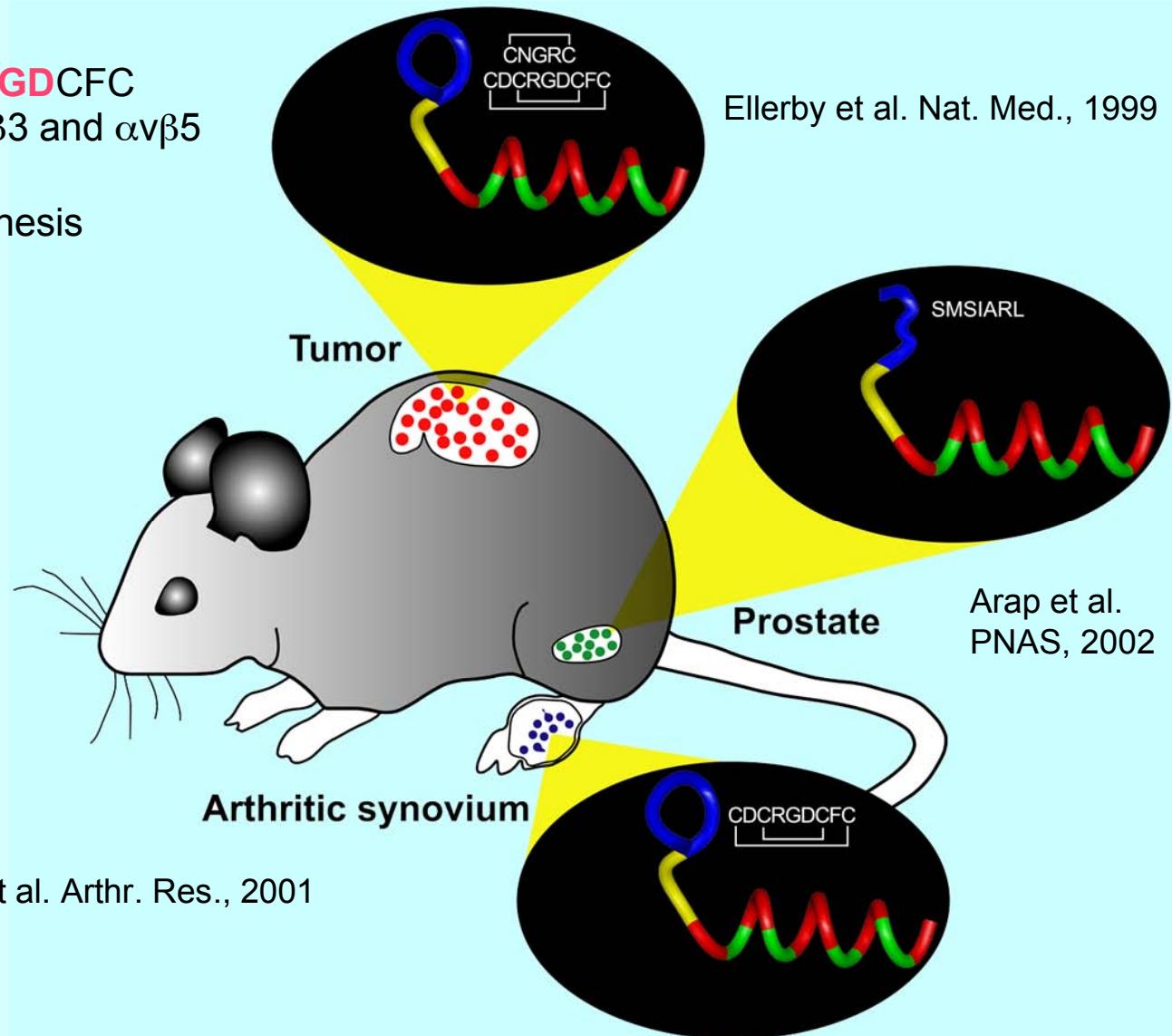


Alitalo et al., 2004

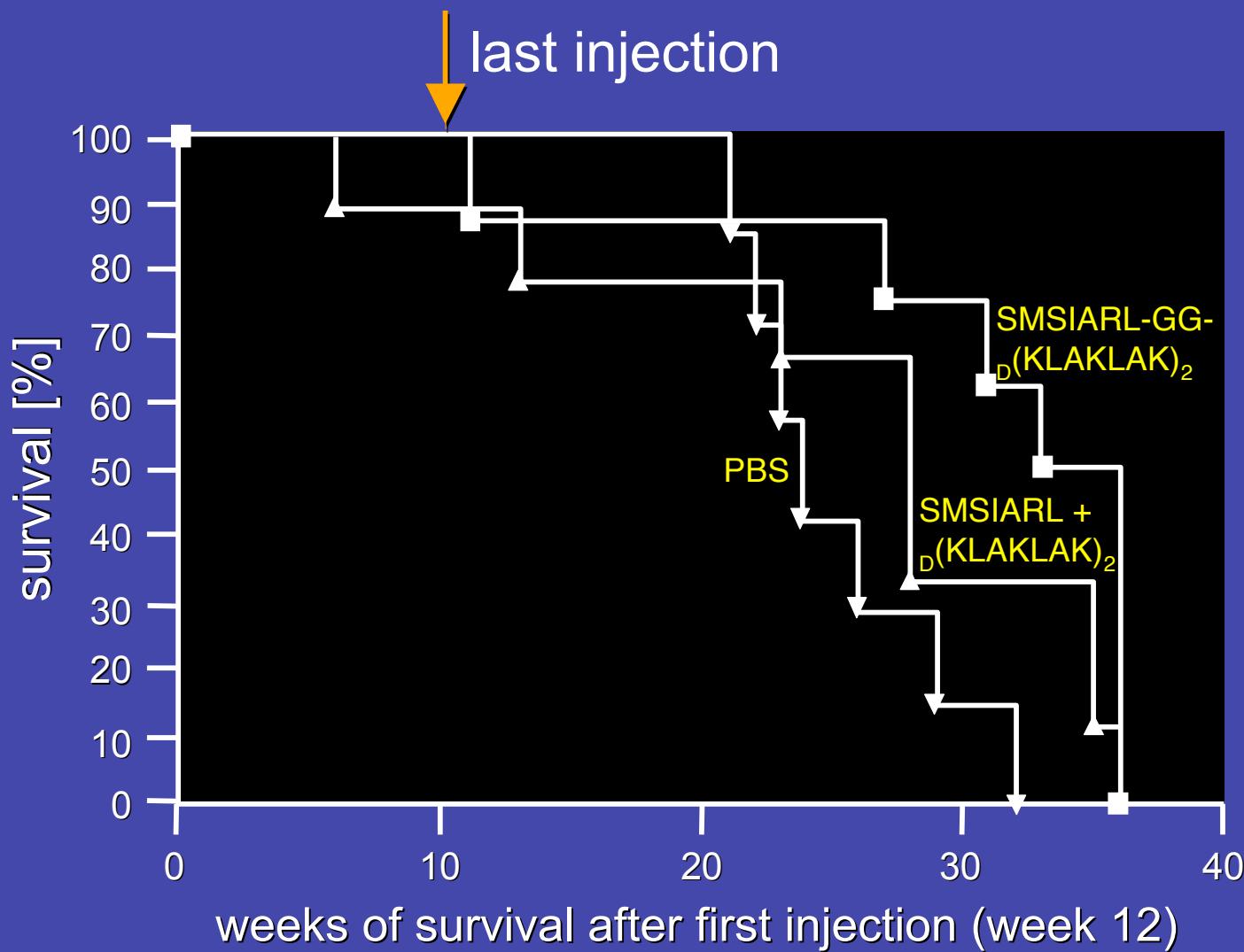
Selective tissue damage by homing peptide-targeted pro-apoptotic peptide _D(KLA)KLAK)₂

RGD-4C = cCDCRGDCFC
Receptor: integrins $\alpha v\beta 3$ and $\alpha v\beta 5$

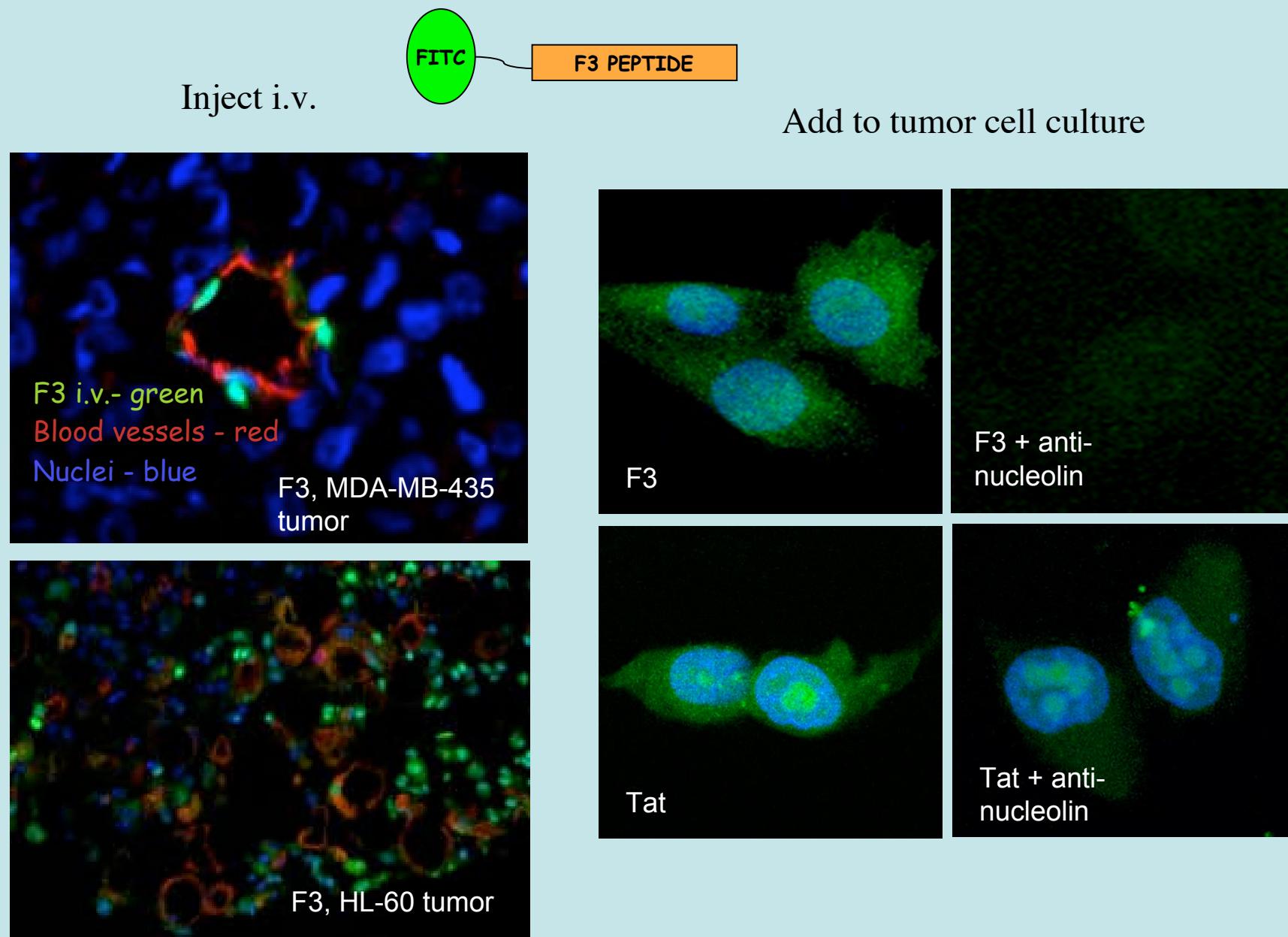
Target: angiogenesis



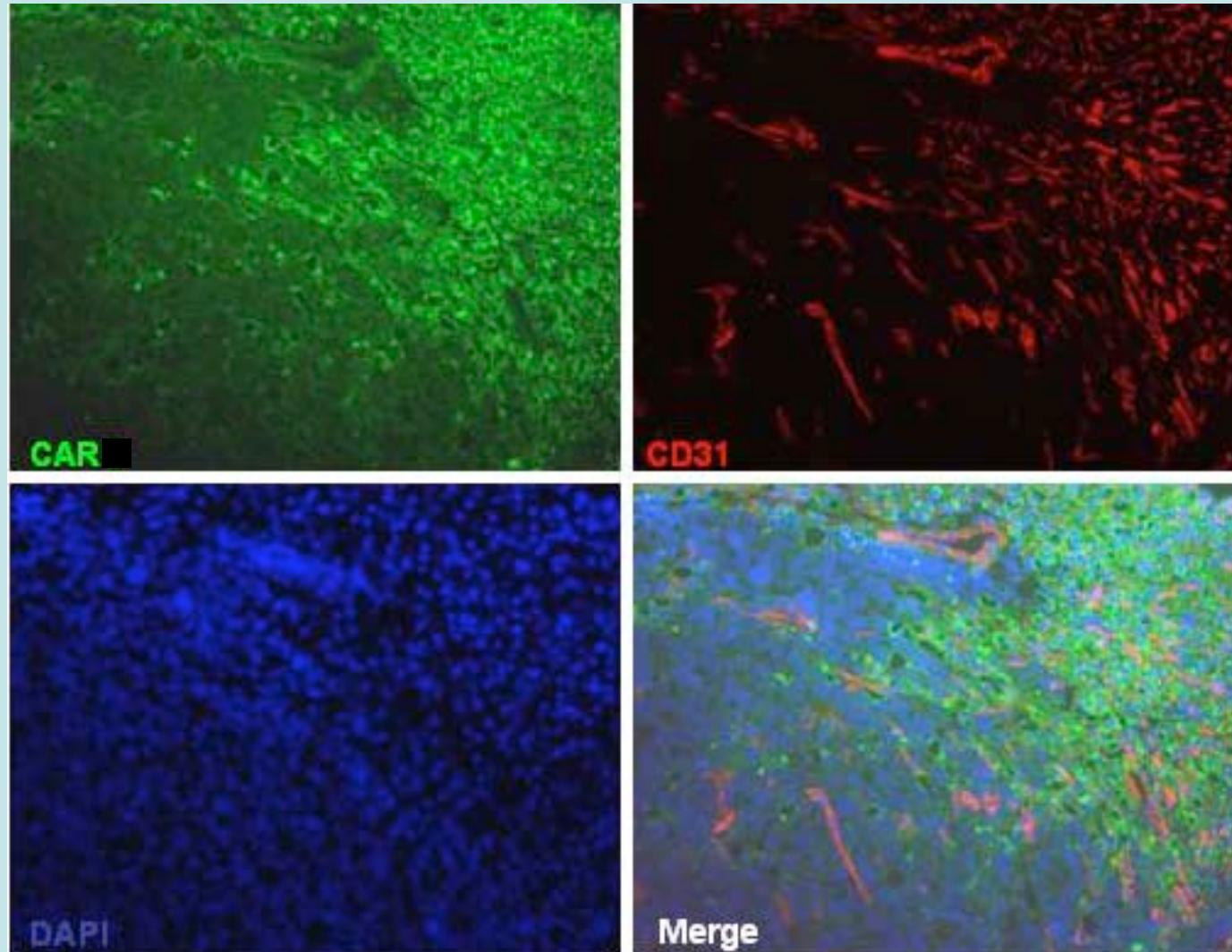
Targeted Preventive Treatment of TRAMP Prostate Cancer Mice



F3 is a cell-penetrating peptide specific for tumor endothelial cells and tumor cells

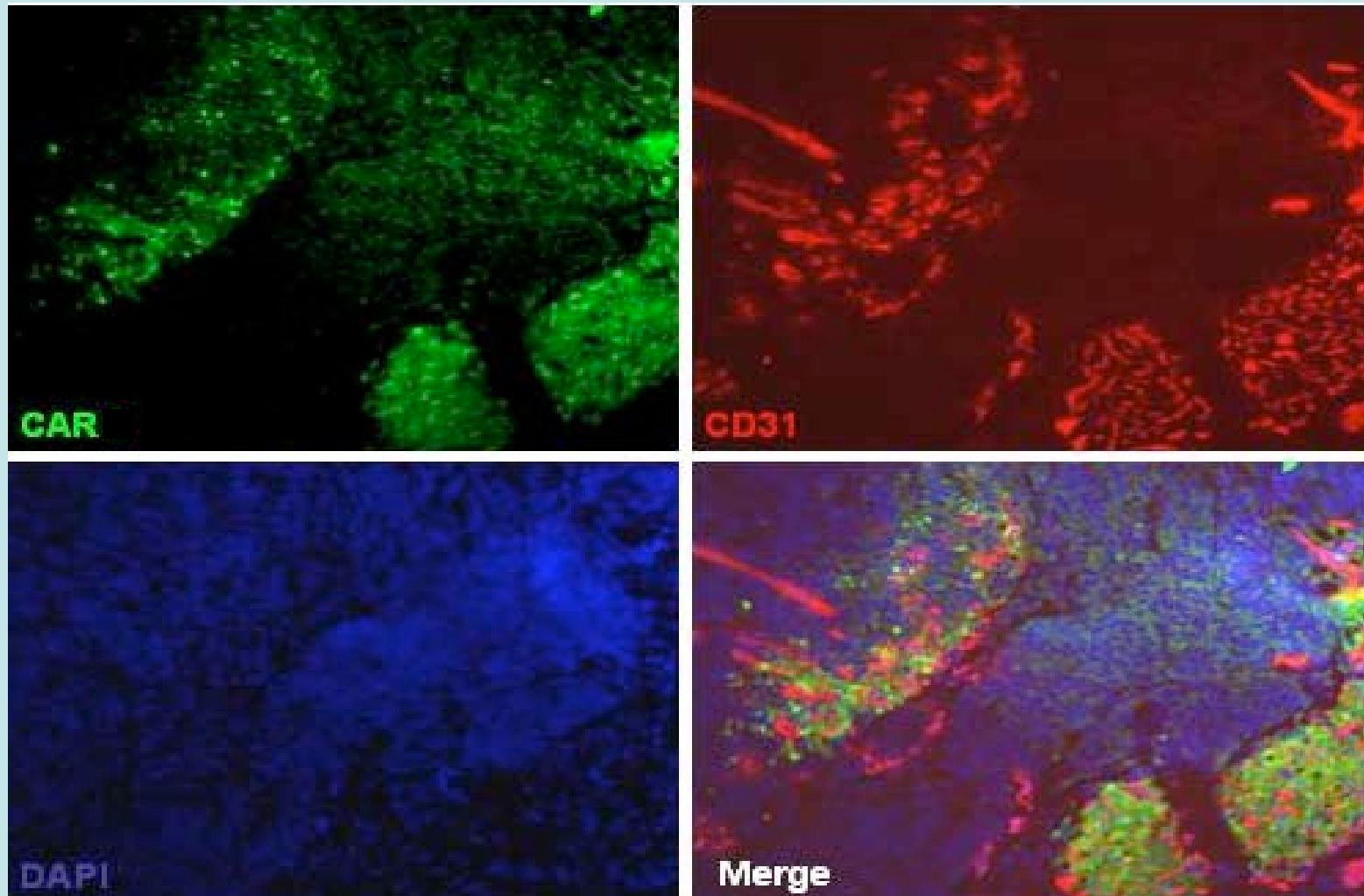


Tumor-homing peptide CAR recognizes tumor vessels
and penetrates into tumor parenchyma (4 hrs)



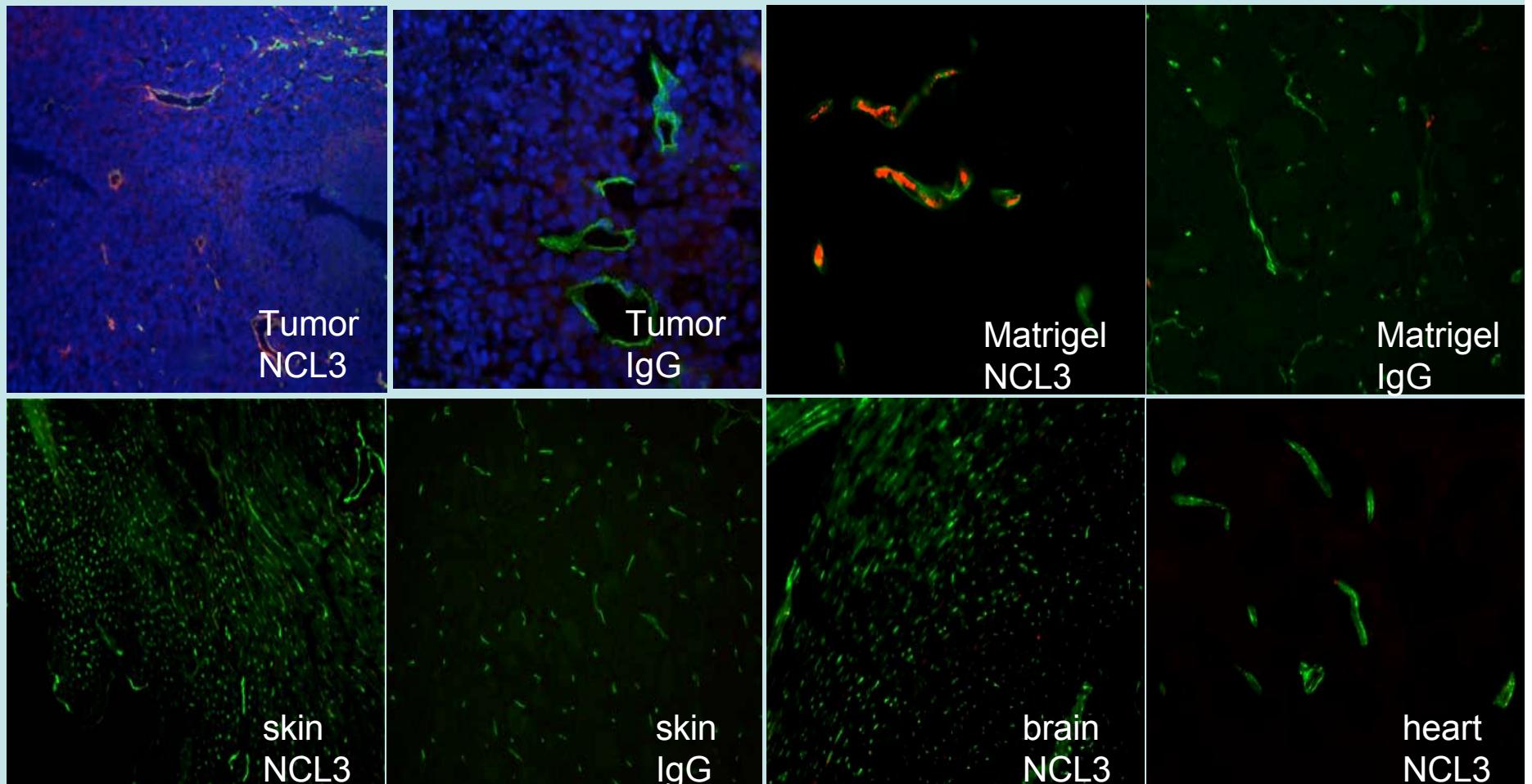
Jarvinen et al.

Tumor-homing peptide CAR recognizes tumor vessels
and penetrates into tumor parenchyma (24 hrs)



Jarvinen et al.

Intravenously injected anti-nucleolin homes to angiogenic blood vessels in tumors and matrigel plugs

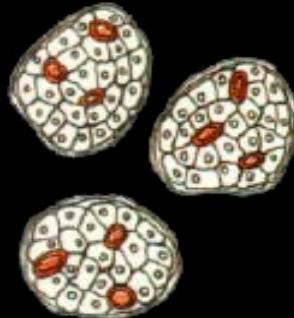


anti-nucleolin; blood vessels; nuclei

Christian et al., 2003

Multistage tumorigenesis in RIP-Tag transgenic mice

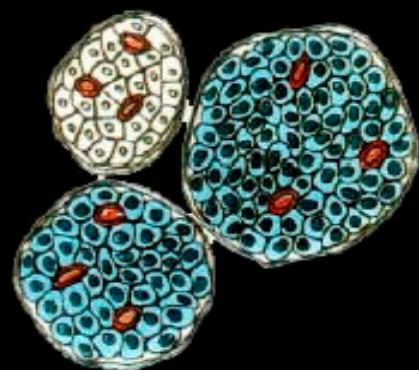
Normal stage
(onc+)



<5 wks

100%

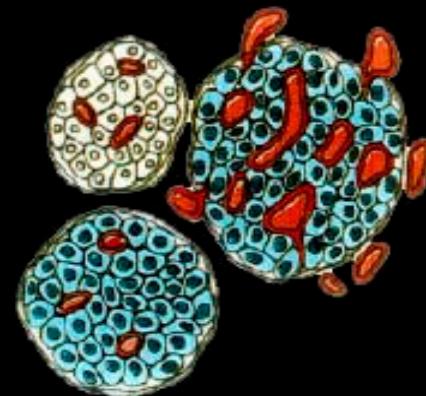
Hyperplastic /
Dysplastic



5-7 wks

~50%

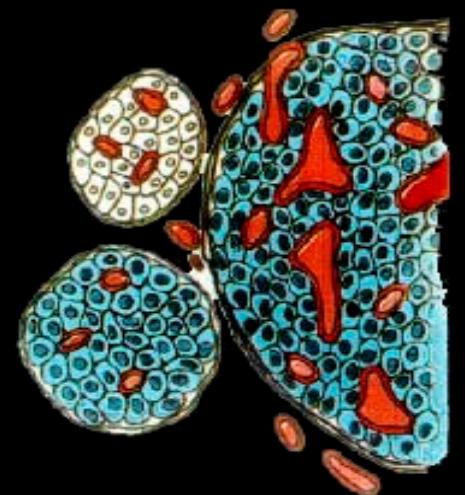
Angiogenic
stage



7-12 wks

~10%

Tumor
stage

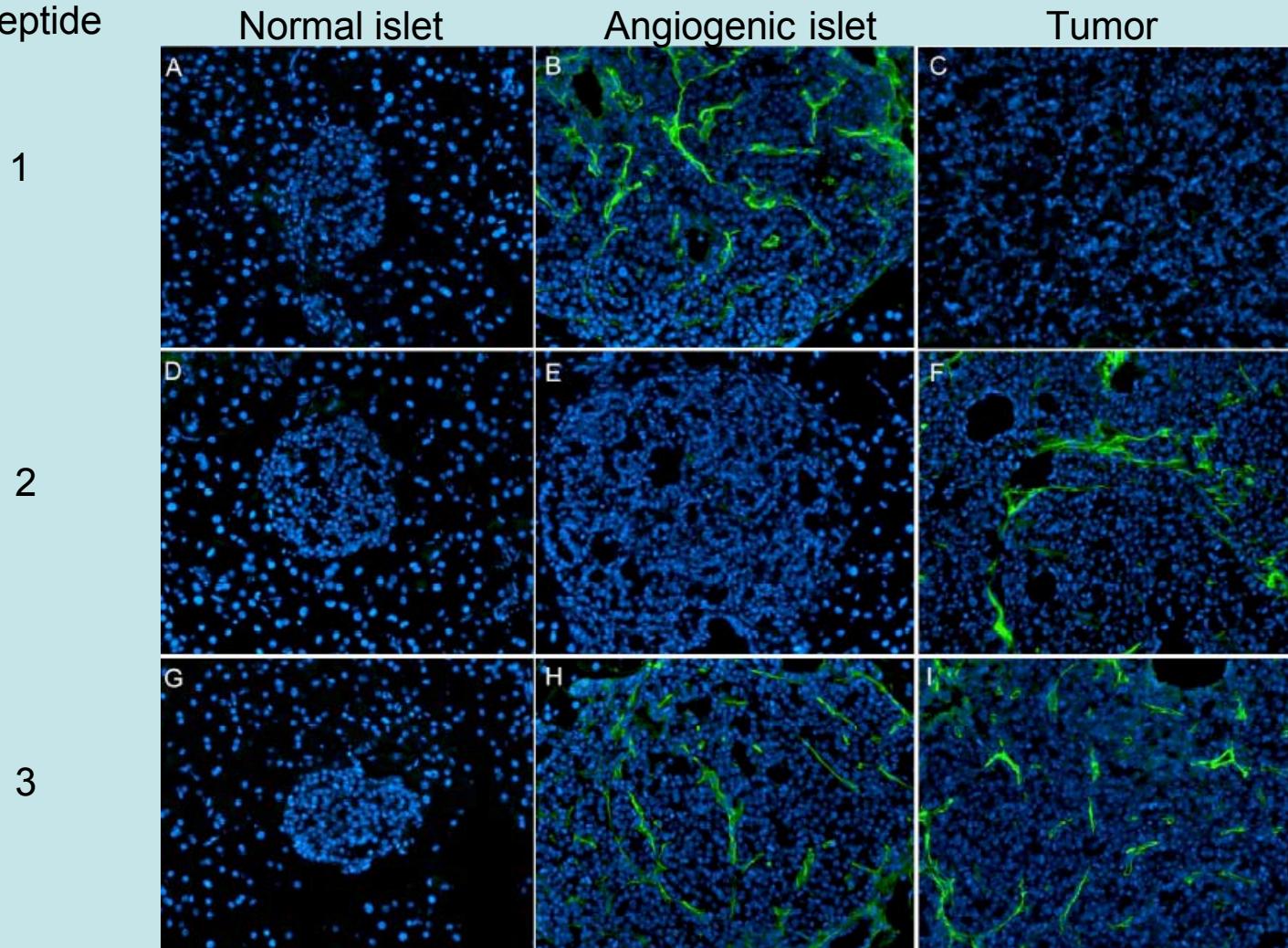


12-14 wks

2-4%

Fluorescein-labeled vascular homing peptides from in vivo phage display reveal blood vessel changes that parallel progression in tumor development

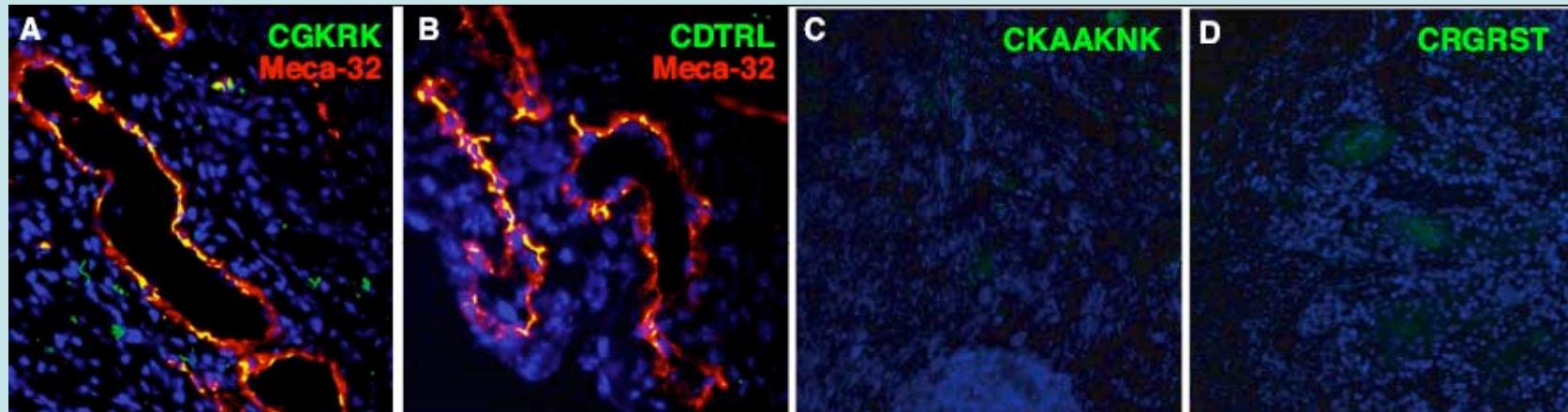
Intravenously
injected peptide



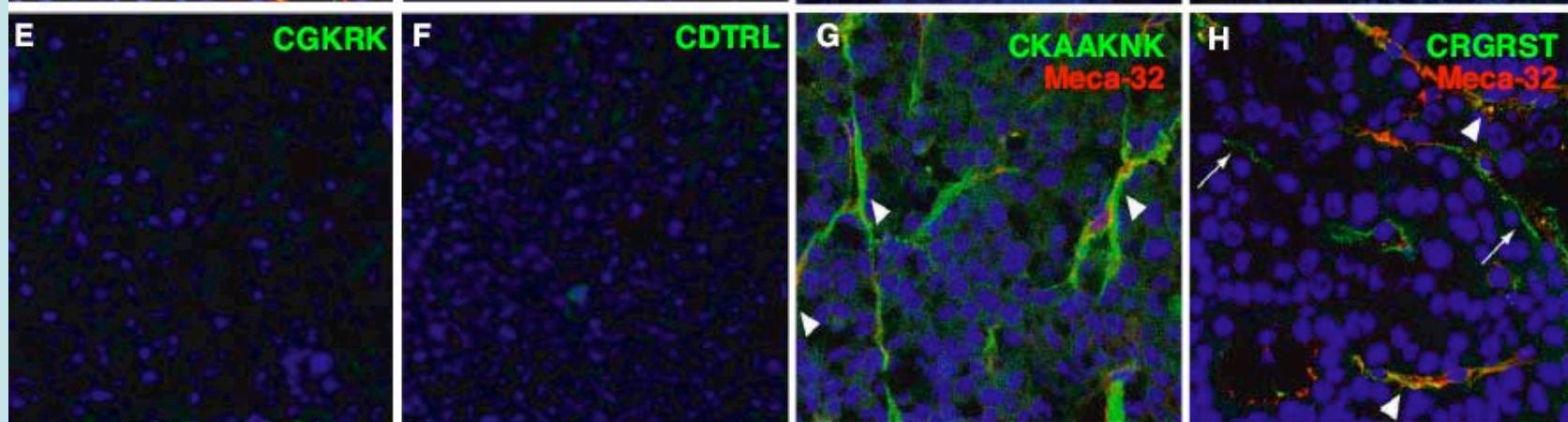
Joyce et al., Cancer Cell, 2003; Hoffman et al., Cancer Cell, 2003

Tumor type-specificity of homing peptides

K14HPV16 Tumors



RIP1-Tag2 Tumors

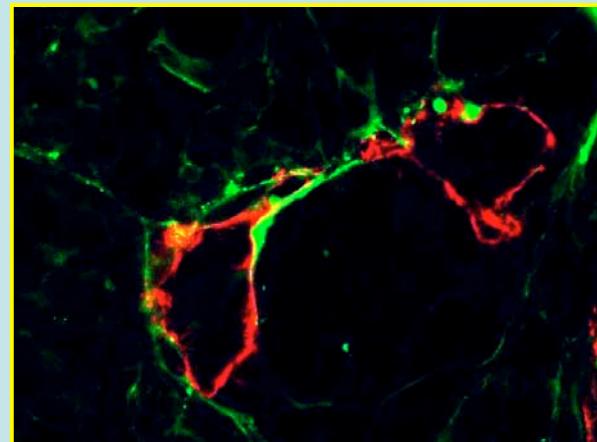


Peptides selected in K14HPV16 tumors

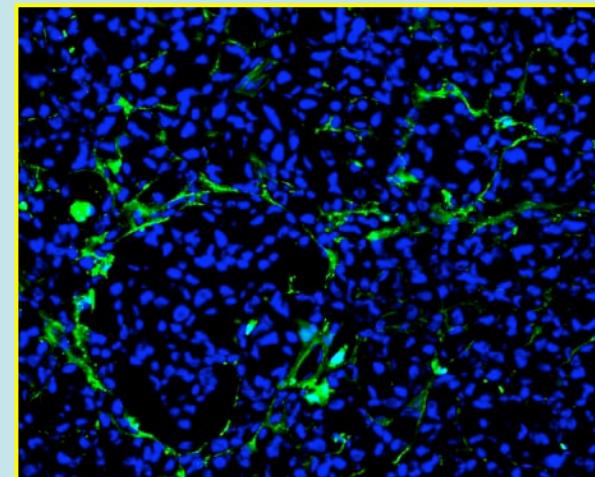
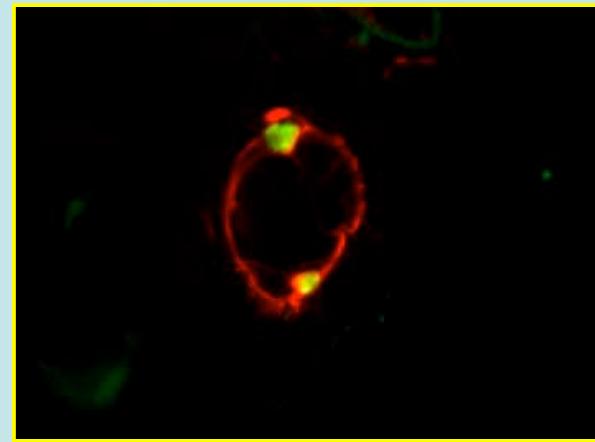
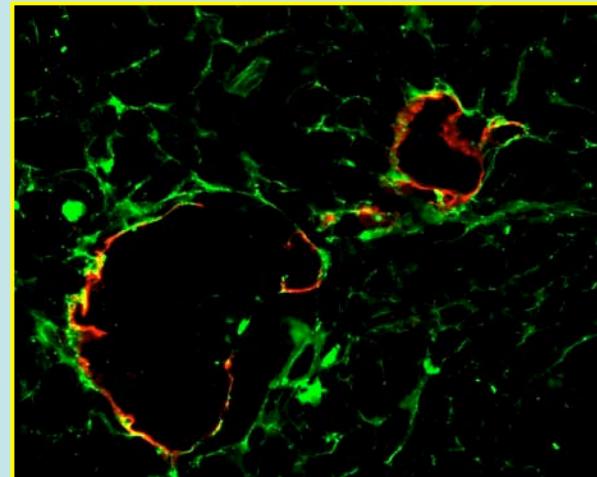
Peptides selected on Rip-Tag tumors

LyP-1 peptide co-localizes with tumor lymphatics

FITC-LyP-1
Podoplanin

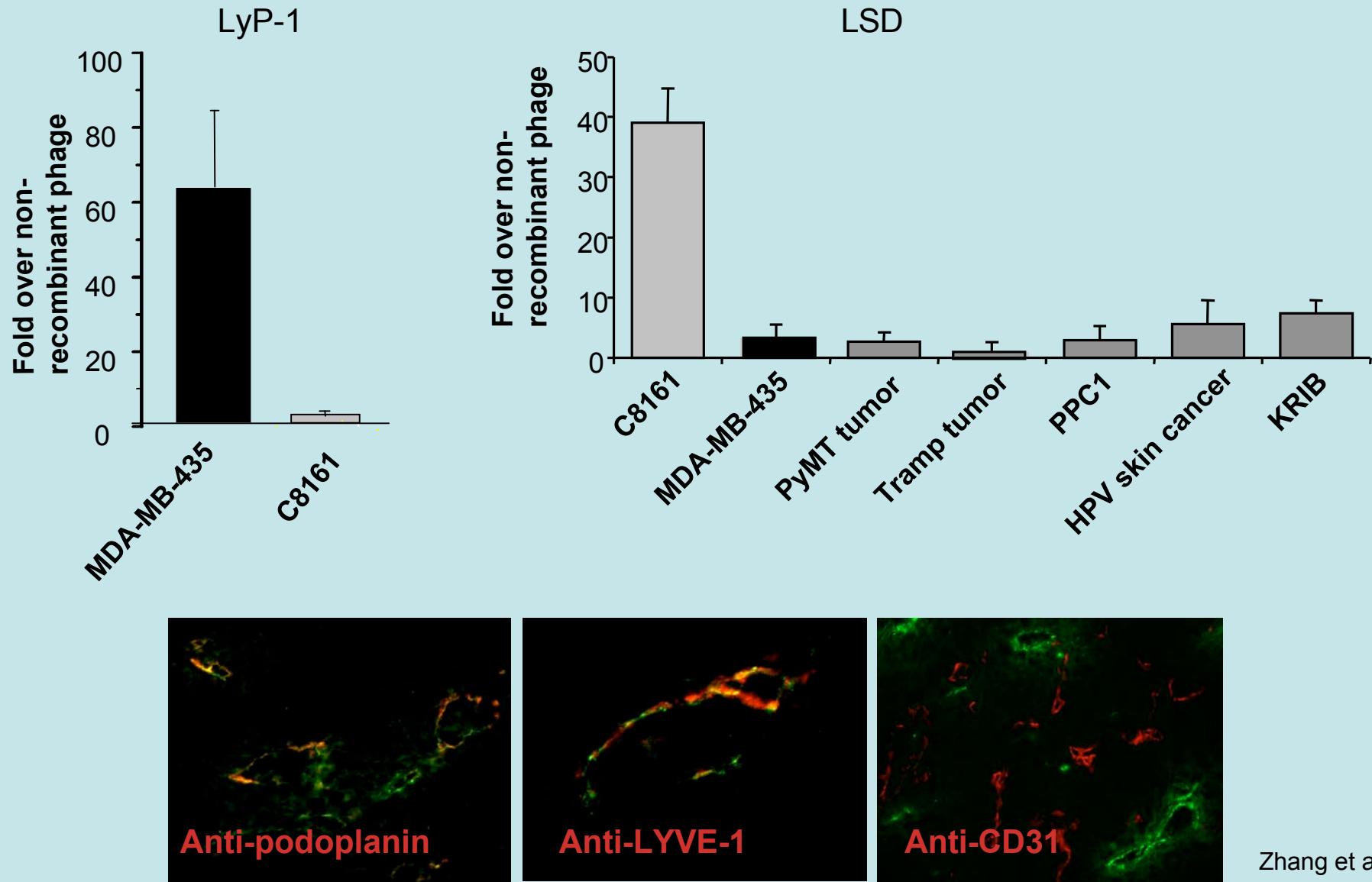


FITC-LyP-1
Lyve-1

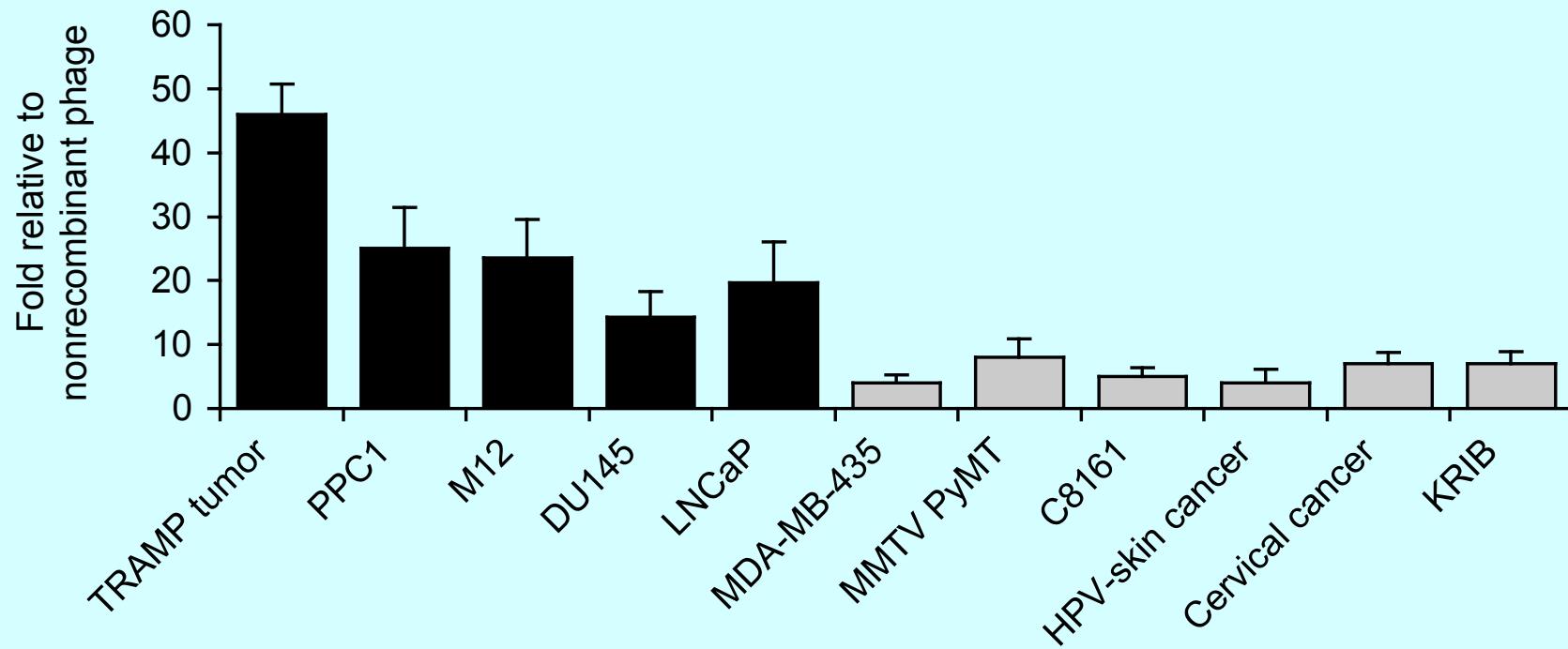


Laakkonen et al., Nature Med., 2002

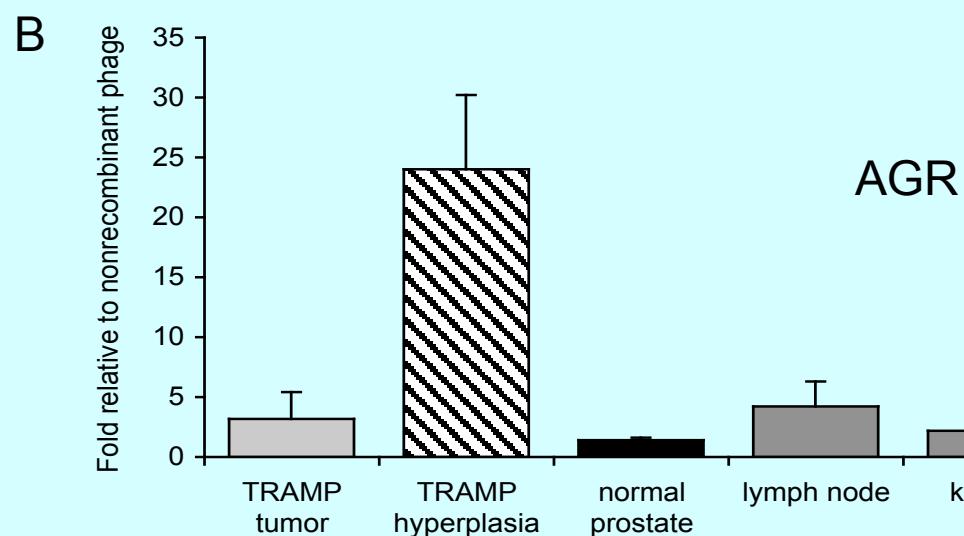
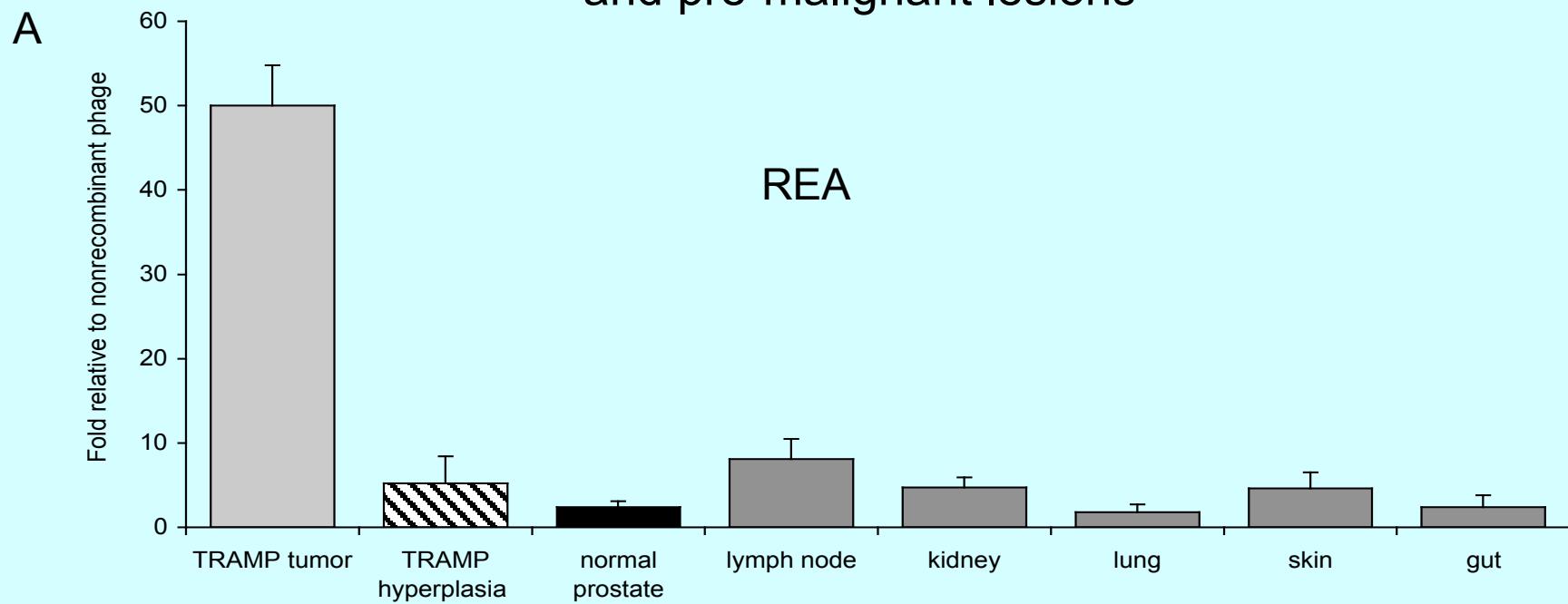
LyP-1 and LSD phage have mutually exclusive tumor type specificities



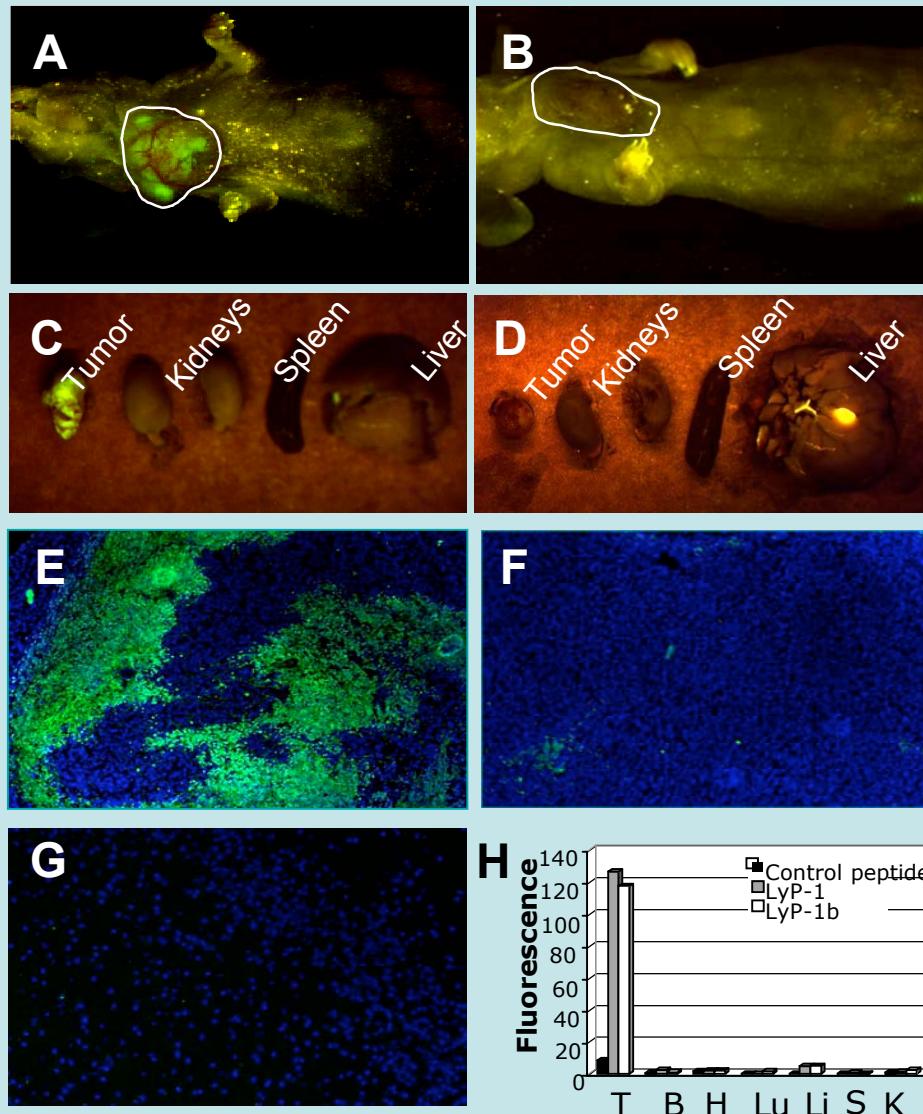
REA selectively recognizes prostate cancer lymphatics



Homing peptides distinguish the lymphatics of cancers and pre-malignant lesions



Homing peptide for tumor lymphatics



Laakkonen et al., PNAS, 2004